

# Experience with Vaccination Against Influenza in the Spring of 1947

## A Preliminary Report \*

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ON the basis of accumulated experience an outbreak of influenza A was anticipated in the winter of 1946-1947. In an effort to gain further information concerning the efficacy of influenza virus vaccine in the prevention of the disease a study was undertaken at the University of Michigan. The vaccine, with expiration date of February, 1947, was received from Army stores through the Service of Preventive Medicine, Office of the Surgeon General. The material had been prepared in the same manner as that utilized in previous studies<sup>1-5</sup> which had demonstrated a prophylactic effect. Its red cell agglutinating titer was 5,120 by a pattern test,<sup>6</sup> the same as that of the standard National Institute of Health control vaccine titrated simultaneously. Immunization of mice demonstrated that its antigenic potency was ten times greater than that required by the National Institute of Health.

### VACCINATION PROGRAM

Through the staff of the Student Health Service, under the acting Directorship of Dr. Margaret Bell, vaccination was offered to the student body on

a voluntary basis. The bulk of the vaccination program was carried out between October 22 and November 2, 1946, and an individual record was prepared for each student. Ten thousand, three hundred and twenty-eight students received vaccine and 7,615 did not. A small number of individuals with marked sensitivity to eggs were excluded. No anaphylactic or other allergic reactions were observed and, according to the records of the Health Service, the number of individuals with systemic complaints was less than 1 per cent.

In case of illness practically all students reported to the Student Health Service where they were seen by physicians who had participated in the studies of previous years and were, therefore, well acquainted with the general diagnostic procedures. A record was kept of all individuals reporting with respiratory infections. Cases suspected to be influenza were studied in relation to etiology.

Early in March, 1947, an increased amount of respiratory disease was observed. At the same time there was an increased incidence of illness with nausea, vomiting, and diarrhea in certain groups. However, the other illnesses appeared to be more characteristic of mild influenza. Only patients with significant fever were admitted to the

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TABLE 1

*University of Michigan 1946-1947 Vaccination Study  
Geometric Mean Antibody Titers before and Two Weeks after Vaccination*

	Subjects	Virus Strains					
		PR8-A		Weiss-A		Lee-B	
		Pre	Post	Pre	Post	Pre	Post
Not Vacc. Prev.	68	38	400	35	271	86	512
Vacc. 1 yr. Prev.*	28	238	420	178	330	297	458
Total Group	96	63	410	59	289	120	497

\* Army veterans vaccinated between October, 1945, and January, 1946

infirmary where further details of history, throat washings, and blood specimens were obtained. As the outbreak increased in scope some of the febrile illnesses were handled as outpatients and others were visited in their residences. From March 3 to April 4 when spring vacation began, 1,359 cases of illness were recorded, an incidence of 7.6 per cent for the period of the outbreak.

During the same period 183 patients were admitted to the infirmary, and from 94 of these materials for virus studies were obtained.

#### ANTIBODY RESPONSE TO VACCINATION

Sera were obtained from 96 individuals before vaccination and 10 days or more after vaccination (Table 1). Sixty-eight of them had not been previously vaccinated and showed excellent responses. Twenty-eight of the group were individuals with clear records of vaccination in the Army approximately one year prior to the present inoculation. It is of interest to observe that their titers before vaccination were still quite high after the interval of one year and that their final level of antibody titer after vaccination did not go beyond that of individuals being vaccinated for the first time. The data indicated, then, that the vaccine had effectively stimulated production of antibody to the strains of virus in the vaccine.

#### VIRUS STUDIES

Great difficulty was encountered in isolating virus from the throat washings

of the patients. Intensive efforts were made to isolate virus in embryonated eggs from the throat washings of 28 patients. Thirteen specimens were investigated by repeated allantoic passages with only negative results. Eight specimens were examined by amniotic inoculation of 10-11 day embryos; all were negative. Ten specimens were inoculated into the amniotic sac of 13-15 day embryos. Six apparently positive results were obtained under these latter conditions. They have not been adapted to allantoic passage, however, and red cell agglutination was demonstrated only with human and guinea pig erythrocytes but not with those of chickens.

Three specimens of throat washings induced characteristic responses in ferrets and were passed in series in that animal. Thence, these strains were adapted to mice and from mice to eggs by the allantoic route. Three additional specimens stimulated antibodies in ferrets. Two were entirely negative. Adaptation of virus to mice after ferret passage was slow and three to five serial passages in the latter species were required before pulmonary lesions were clearly observed. The difficulty in establishing virus in eggs is quite different from our previous experience with influenza A.

*Serological evidence* indicates that the virus is a strain of influenza virus, Type A. The majority of patients recovering from the illness showed increased antibody titers to the PR8 strain and to a newly isolated strain

TABLE 2

*Comparison of Mean Antibody Titers in Acute and Convalescent Phase Sera of Hospitalized Patients*

Group	Number	Serum	Virus Strains			
			PR8		Rhodes	
			Titer	Difference	Titer	Difference
Unvacc.	39	Acute	76		27	
		Conv.	230	3.0X	120	4.4X
Vacc.	55	Acute	499		32	
		Conv.	809	1.6X	115	3.6X

TABLE 3

*Comparison of Individual Responses to PR8 and 1947 Strain of Influenza Virus, Type A*

	PR8		Rhodes—1947	
	Acute	Conv.	Acute	Conv.
1947 Illness				
Ben	64	128	32	256
S. one	64	512	<32	64
Tier	256	2,048+	32	1,024
1946 Vaccinated	Pre	Post	Pre	Post
Senc	<32	8,192	<32	64
Yager	32	2,048	<32	<32
Dioz	<32	8,192	<32	<32
Dens	32	8,192	<32	2,048+
1943 Illness	Acute	Conv.	Acute	Conv.
Cope	<32	4,096	<32	<32
Chap	32	1,024	<32	<32
Poul	64	1,024+	<32	128

(Rhodes). The mean acute and convalescent titers in unvaccinated individuals were 76 and 230, respectively, for PR8; 27 and 120, respectively, for Rhodes (Table 2). It is of interest to point out that the mean titers in the acute stage of illness were 76 in the unvaccinated and 499 in the vaccinated when tested against PR8. This latter figure is essentially the same as that of the group tested 2 weeks after vaccination, indicating that there had been no sharp loss of antibody level in the interval since vaccination. In sharp contrast, however, there was no significant difference in the low titers of vaccinated and unvaccinated individuals in the acute stage of illness when tested with the new strain. It was of further interest that when comparing the titers of sera from individuals before and after vaccination in 1946, the majority showed a good rise to PR8 and Weiss strains which were included in the vac-

cine but little increase in antibody to the new strain (Table 3). Further tests with acute and convalescent sera from patients suffering from influenza A in 1943 showed a sharp increase in titer to the PR8 strain with little or slight antibody production to the current new strain. These results clearly indicate that the strain prevalent in this outbreak has a sharp antigenic difference from those commonly encountered in previous years and from those incorporated in the vaccine.

#### INCIDENCE OF ILLNESS IN VACCINATED AND UNVACCINATED INDIVIDUALS

The amount of respiratory disease that occurred in vaccinated and unvaccinated persons during the period of the outbreak is shown in Table 4. That the major proportion of cases was due to the influenza virus was indicated by positive serological evidence of infection in approximately 80 per cent of the

TABLE 4

*Comparison of Incidence of Respiratory Disease in Vaccinated and Unvaccinated Individuals*

	Vaccinated (10,328)		Unvaccinated (7,615)	
	No. of Cases *	Incidence Per cent †	No. of Cases *	Incidence Per cent †
Inpatients	88	0.85	85	1.12
Outpatients	616	5.96	489	6.42
Room Calls	39	0.38	42	0.55
Total	743	7.19	616	8.09

\* Number of cases in interval March 3–April 4, 1947.

† Based on the assumption that the populations under study remained unchanged in the interval between vaccination and the outbreak. Actually a slight but comparable reduction occurred in both vaccinated and unvaccinated groups.

94 hospitalized patients. It is clearly evident from the data that the incidence of disease was no different in vaccinated and unvaccinated individuals.

#### INTERPRETATION

In view of the laboratory studies indicating that the antibody titer for the new strain was essentially the same in vaccinated and unvaccinated persons, it is not surprising that the amount of illness was practically the same. Since the antibody titers to the strains of virus in the vaccine were high in the vaccinated individuals who became ill, it seems unlikely that the ineffectiveness of the vaccine in the prevention of influenza in this instance was related to the interval of time between vaccination and the appearance of the outbreak.

All the data point to the probability that the antigenic deviation of the virus encountered is the responsible factor. This is further supported by the evidence obtained with ferret sera. The sera of ferrets inoculated with the new strains ordinarily developed high titers to recent (1947) strains isolated here and also to some furnished by Dr. J. E. Smadel of the Army Medical School, but had decidedly less response to the PR8 and Weiss strains of Type A. Convalescent sera from ferrets inoculated with these two latter strains also exhibited high titers to them with little or low titers to the new strains. More-

over, some presumably normal ferret sera were found to neutralize the new strains in eggs and mice; the interpretation of this has not been fully established.

Thus, the absence of effect of vaccination during the outbreak of influenza in the spring of 1947 appears to be due to the lack of sufficient antigenic crossing between the strains of virus in the vaccine and the prevalent strain responsible for the epidemic. The implications of this and other observations will be discussed in a more detailed report to be published.

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